

## Statistical Consult for NDA 21-229

### NDA 21-229

**Name of Drug:** Prilosec (omeprazole)

**Applicant:** Proctor and Gamble Co.

**Indication:** Treatment of Heartburn

**Documents Reviewed:** Electronic documents for use studies (003, 014, 022, 067, 091) submitted by sponsor on 1/27/00 and 4/25/00.

**Medical Reviewer:** Dr. Ling Chin and Dr. Daiva Shetty

**Statistical Consultant:** Laura Lu, Ph.D.

**Date of Review:** 9/11/00

### I. Introduction

The sponsor conducted a total of 5 OTC use studies (Studies 003, 014, 022, 067, 091) to assess consumer compliance. These are uncontrolled studies with one-arm (omeprazol). Study 003 was the primary actual use study with 1514 patients recruited and 1093 patients participated. The primary objective of these studies was to characterize the usage patterns/dosing compliance of omeprazole magnesium when used according to proposed label instructions under naturalistic OTC conditions. Per Dr. Ling Chin's request, this statistical consult provides comments for Study 003. Comment #3 also applies to Studies 022 and 067.

### II. Statistical Comments

#### 1. Confidence Intervals

The primary information for compliance provided by the sponsor was the consistency (with label in terms of dosing compliance) rates among the patients who took at least one dose of medication and had complete data. Confidence intervals are more informative than the a single rate estimation by providing a range for the estimation rate based on estimation error. Therefore, this reviewer presents the 95% confidence intervals for the consistency rate in overall and prevention/relief patient populations for the actual use study 003 in Table 1 below. According to the company, a total of 815 patients had compliance status (consistent or inconsistent) with 812 of these from the completer's group and 3 of these from the incompleter's group. But it is not sure how these 815 patients were associated with the detailed patient disposition groups presented in Table 1a in Appendix A.

**Table 1. Point Estimation and Confidence Intervals for Consistency Rate  
(Study 003)**

	Prevention Any Time (N = 36)	Prevention 1 hr Before (N = 28)	Dual Prevention (N = 13)	Relief (N = 316)	Prevention And Relief (N = 422)	Overall (N = 815)
<b>Consistency (n (%))</b>	9 (25%)	9 (32%)	7 (54%)	254(80%)	228 (54%)	507 (62%)
<b>95% Confidence Interval</b>	(11%, 39%)	(15%, 49%)	(27%, 81%)	(76%, 84%)	(49%, 59%)	(59%, 65%)

## 2. Lost-to-Follow-up Patients

In Study 003, a total of 210 patients were lost to follow-up (see Table 1a in Appendix A) without returning the product use journal, so no information was available in actual use pattern. Among the baseline characteristics, frequency of heartburn during day time in the past, frequency of heartburn during night time in the past, Rx medication use (whether Rx medication was used for heartburn before), and medication factor (whether medication was a factor contributing to heartburn in the past) were strongly associated with consistency rate ( $p=0.001$ ). Detailed results presented in Tables a2-a5 in Appendix A show that consistency rate decreases as the frequency of heartburn increases, and the consistency rate is lower among patients who used Rx heartburn medication before and among patients whose heartburn was contributed by use of medication. To assess the potential difference in consistency rates among the lost-to-follow-up patients and the completers, the distribution of heartburn frequency, Rx medication use and medication factor among the completers and lost-to-follow-up patients were compared in Tables 2-5 below. Tables 2 and 3 below show that the lost-to-follow-up patients tend to have heartburn less frequently compared with the completer group. Tables 4-5 show that the proportion of patients who used Rx medication before and the proportion of patients whose heartburn was contributed by use of medication were less among lost-to-follow-up patients than that of the completer group. So based on association between baseline characteristic and consistency rate, there is no evidence showing that the consistency rate in the lost-to-follow-up patients were lower than that in the completer group. However, since the consistency rate could be influenced by unobserved factors such as reason for taking the medication, there is still chance that the consistency rate in the lost-to-follow-up group is lower than that in the completer's group.

**Table 2. Distribution of Frequency of Heartburn During Daytime (Study 003)**

Patient Population	Frequency of Heartburn During Daytime				
	Rarely	1	2-3	4-5	$\geq 6$
Completer (N=874)	170 (19.5%)	174 (19.9%)	319 (36.5%)	101 (11.6%)	110 (12.6%)
L-T-F-U (N=210)	83 (39.5%)	52 (24.8%)	57 (27.1%)	11 (5.2%)	7 (3.3%)

\*: Lost-to-follow-up patients

**Table 3. Distribution of Frequency of Heartburn During Nighttime (Study 003)**

Patient Population	Frequency of Heartburn During Nighttime				
	Rarely	1	2-3	4-5	$\geq 6$
Completer (N=874)	298 (34.1%)	160 (18.3%)	267 (30.6%)	77 (8.8%)	72 (8.2%)
L-T-F-U (N=210)	103 (49.1%)	47 (22.4%)	40 (19.1%)	15 (7.1%)	5 (2.4%)

\*: Lost-to-follow-up patients

**Table 4. Distribution of Rx Medication Use (Study 003)**

Patient Population	Rx Medication Use	
	Yes	No
Completer (N=874)	95 (10.9%)	779 (89.1%)
L-T-F-U (N=210)	8 (3.8%)	202 (96.2%)

\*: Lost-to-follow-up patients

**Table 5. Distribution of Medication Factor (Study 003)**

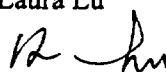
Patient Population	Medication Factor	
	Yes	No
Completer (N=874)	26 (3.0%)	848 (97.0%)
L-T-F-U (N=210)	0 (0.0%)	210 (100.0%)

\*: Lost-to-follow-up patients

### 3. Analyses Based on Predominant Use Groups

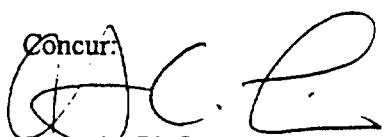
Consistency rates were also provided by predominant use groups (where predominant use is defined as using the study medication more than 50% of the time for anyone of the three reasons for use: 1) predominant Prevention-Any-Time users, 2) predominant Prevention-1-Hour-Before users, 3) predominant Relief users, and 4) no predominant use (includes those subjects who did not use the study medication more than 50% of the time for any one of the three reasons for use)). Since the analyses based on predominant use groups were not prespecified and there is no clear rationale for this reclassification, judgement should be based on the results from the prespecified analyses based on strict prevention/relief groups.

Laura Lu



Mathematical Statistician

Concur:



Stan Lin, Ph.D.

Team Leader

9/13/00

CC:

HFD-180/Walsh

HFD-560/Keravich

HFD-560/Chin/Shetty/Katz/Ganley

HFD-560/Div. File

HFD-725/Lu/Lin ST./Huque

HFD-725/Div. File

## Appendix A

**Table 1a. Patient Disposition in Study 003**

<b>Reason for Discontinuation</b>	<b>N</b>
Received Study Medication and Product Use Journal	1093
Completed Study	874
Took at Least 1-Dose Medication	822
Did Not Take Medication	52
Did Not Complete Study	219
Adverse Event	4
Subject Reconsidered/Withdrew Consent	4
Lost to Follow-Up	210

**Table 2a. Frequency (Daytime) BY Consistency Status**

Heartburn History: Frequency During Daytime  
Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct	N	Y	Total
2-3	109 13.37 35.05 35.39	202 24.79 64.95 39.84	311 38.16
4-5	50 6.13 50.00 16.23	50 6.13 50.00 9.86	100 12.27
>=6	75 9.20 70.09 24.35	32 3.93 29.91 6.31	107 13.13
ONCE	37 4.54 23.87 12.01	118 14.48 76.13 23.27	155 19.02
RARELY	37 4.54 26.06 12.01	105 12.88 73.94 20.71	142 17.42
Total	308 37.79	507 62.21	815 100.00

P-value from Chi-Square Test: 0.001

**Table 3a. Frequency (Night) BY Consistency Status**

Heartburn History: Frequency During Night  
Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct	N	Y	Total
2-3	110 13.50 43.14 35.71	145 17.79 56.86 28.60	255 31.29
4-5	32 3.93 42.11 10.39	44 5.40 57.89 8.68	76 9.33
>=6	47 5.77 65.28 15.26	25 3.07 34.72 4.93	72 8.83
ONCE	38 4.66 25.85 12.34	109 13.37 74.15 21.50	147 18.04
RARELY	81 9.94 30.57 26.30	184 22.58 69.43 36.29	265 32.52
Total	308 37.79	507 62.21	815 100.00

P-value from Chi-Square Test: 0.001

**Table 4a. Rx Medication Use By Consistency Status**

Heartburn History: Rx Medication Use (Y=Yes, N=No)  
Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct	N	Y	Total
N	253 31.04 34.94 82.14	471 57.79 65.06 92.90	724 88.83
Y	55 6.75 60.44 17.86	36 4.42 39.56 7.10	91 11.17
Total	308 37.79	507 62.21	815 100.00

P-value from Chi-Square Test: 0.001

**Table 5a. Medication Factor By Consistency Status**

MEDICAT(Heartburn Factor: Medication, 1=Yes, 2=No)  
Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct	N	Y	Total
1	18 2.21 72.00 5.84	7 0.86 28.00 1.38	25 3.07
2	290 35.58 36.71 94.16	500 61.35 63.29 98.62	790 96.93
Total	308 37.79	507 62.21	815 100.00

P-value from Chi-Square Test: 0.001



NDA 21-229

HFD-560 Division Files

HFD-180 Division Files

HFD-560 Ganley/Katz/ Shetty/Chin/Cothran

HFD-180 Walsh